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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,338	11/14/2000	Yoshiyuki Ueno	1110-0279P	3959

7590 10/18/2005

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/700,338	**Applicant(s)** UENO, YOSHIYUKI	
	Examiner Ulrike Winkler	**Art Unit** 1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 August 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *9/28/2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *8 and 17*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: Note attached 892.

DETAILED ACTION

The After Final Amendment filed August 25, 2005 in response to the Office action of March 29, 2005 is acknowledged. The amendment has been entered because the amendment is deemed to place the claims in better condition for appeal by materially reducing and clarifying the issues. Claims 10-13 and 18 have been cancelled. Claims 8 and 17 are pending.

Claim Rejections - 35 USC § 103

The rejection of claims 8 and 17 under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Nature of Medicine, 1997, cited in 892 of paper No. 7), Harada et al. (Hepatology 1997, see IDS 11/14/2000) and Shirakawa et al. (U.S. Pat. No. 6,114,507, cited in 892 of paper No. 7) **is maintained** for reasons of record.

The following references have been cited in the response to Applicants arguments. The references evidence the state of the art at the time the invention was made: Kuroki et al., (Virchows Archives 1996, cited in IDS of March 16, 2001), Graham et al., (European Journal of Gastroenterology and Hepatology 1998, Vol. 110, pages 553-557, filed with applicants reply of May 8, 2003), Crawford J.M., Chapter 18 The liver and the biliary tract, in Robbins Pathologic Basis of Disease, 5th ed. 1994, W.B. Saunders Company, Philadelphia, PA, cited in 892 paper No. 03082005), and J. A. Trapani (International Review of Cytology, 1998, Vol. 182, cited office action in 892 of paper No. 03082005).

Applicants' arguments and the Offices response are essentially the same of record.

The combined teaching of Harada et al. and Kondo et al. indicate that although there are two apoptotic mechanism available to cells, in liver injury only the Fas/Fas ligand mechanism is

implicated. The references show that blocking the Fas/Fas ligand mechanism is sufficient to be preventative. It was known in the prior art that biliary epithelial cells express Fas and that the Fas/Fas ligand system is involved in the PBC. Based on what was known in the prior art the ordinary artisan would have had a high expectation of success in treating a patient with an anti-Fas ligand antibody. Shirakawa et al. teaches a broad method of treating a systemic or topical pathological condition, caused by an abnormality of the Fas/Fas ligand system. The treatment method involves administering an anti-Fas ligand antibody to a patient. Employing the method of Shirakawa et al. the administration of anti-Fas ligand antibody would systemically treat all Fas/Fas ligand interactions in the entire body. The ordinary artisan would have been motivated to use the antibody for the treatment of PBC because apoptosis has been implicated in that disease. The ordinary artisan would have had a high expectation of success in administering the antibody to a patient as set out in the combined references of Harada et al., Kondo et al. and Shirakawa et al. The rejection is maintained for reasons of record.

The rejection of claims 8 and 17 under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Nature of Medicine, 1997, cited in 892 paper No. 7), Harada et al. (Hepatology 1997, see IDS) and Shirakawa et al. (U.S. Pat. No. 6,114,507) as evidenced by Galle et al. (Journal of Experimental Medicine, 1995, cited in 892 paper No. 07202004), Dienes et al. (Virchows Archives, 1997, cited in 892 paper No. 07202004) and Luo et al. (Journal of Viral Hepatitis, 1997, cited in 892 paper No. 07202004) **is maintained** for reasons of record.

The following references have been cited in the response to Applicants arguments. The references evidence the state of the art at the time the invention was made: Kuroki et al.,

(Virchows Archives 1996, cited in IDS of March 16, 2001), Graham et al., (European Journal of Gastroenterology and Hepatology 1998, Vol. 110, pages 553-557, filed with applicants reply of May 8, 2003 and cited in 892 of the instant response), Crawford J.M., Chapter 18 The liver and the biliary tract, in Robbins Pathologic Basis of Disease, 5th ed. 1994, W.B. Saunders Company, Philadelphia, PA, cited in 892 of paper No. 03082005), and J. A. Trapani (International Review of Cytology, 1998, Vol. 182, cited office action in 892 of paper No. 03082005).

Applicants' arguments and the Offices response are essentially the same of record.

The combination of references of Kondo et al., Harada et al. and Shirakawa et al. has been discussed above. The general teaching in the prior art is that anything that causes the loss of hepatocytes and subsequent regeneration of the hepatocytes results in the formation of cirrhosis. The involvement of an immune based mechanism in the etiology of PBC was known in the prior art (see Kuroki et al., 1996 and Crawford J.M 1994). At the time the invention was made it was known in the art that the initial injury in PBC is caused by the destruction of portal bile ducts (see Kuroki et al., Virchows Archives 1996, IDS March 16, 2001). Epithelial cells of the bile duct express Fas antigen. The Fas antigen is important in the death of biliary epithelial cells via the apoptotic pathway (see Kuroki et al., Virchows Archives 1996, IDS March 16, 2001). Based on what is generally known in the prior art Applicants' argument that it might be desirable to induce apoptosis with an agonist (induce Fas mediated apoptosis) is not convincing since cell death of epithelial cells in the biliary duct leads to disease. There are only two mechanism for inducing apoptosis one is through the secretory mechanism involving Ca2+ dependent perforin mediated lyses which is CD8+ T cell response and the other is through the nonsecretory pathway which uses the Fas/Fas ligand interaction. Based on the totality of the

references it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat primary biliary cirrhosis by disrupting the Fas/Fas ligand interaction that leads to apoptosis of the cells involved in primary biliary cirrhosis as taught by Harada et al. The ordinary artisan would have been motivated to use the antibody for the treatment of PBC because apoptosis has been implicated in that disease. The ordinary artisan would have had a high expectation of success in administering the antibody to a patient as set out in the combined references of Harada et al., Kondo et al. and Shirakawa et al. The rejection is maintained for reasons of record.

Conclusion

No claims allowed.

Information Disclosure Statement

The listing of references in a response is not a proper information disclosure statement. Graham et al., Bile duct cells in primary biliary cirrhosis are primed for apoptosis. European Journal of Gastroenterology and Hepatology, 1998, Vol. 10, pp 553-557 was filed with applicants reply of May 8, 2003. The reference was not cited on a 1449 form. The reference is cited on an 892 form in the instant response solely to ensure that the reference become part of the Official record.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 10/17/05